REMARKS

This Amendment is filed in response to the final office action dated July 26, 2007. Claims 1-3 and 6-8 are pending in the application. Claims 4-5 and 9-32 have been canceled without prejudice to Applicants' right to prosecute them in one or more divisional applications. Applicants gratefully acknowledge that Claims 3 and 7 are considered free of art. Claims 1 and 6 have been amended to clarify that they are directed to RNA polynucleotides antisense to a sequence comprising the glucosylceramide synthase mRNA. Support for the amendment can be found at page 9, lines 17-19 and page 10, lines 11-12 & 13-24, for example. It is believed that no new matter has been added by way of amendment.

Claims 1-2, 6 and 8 stand rejected under 35 U.S.C. § 102(a) as being anticipated by *Deng*, as evidenced by *Nieda*, and *Balreira*. Applicants request that the rejection be reconsidered and withdrawn for the following reasons. Specifically, *Deng* lacks any disclosure of a composition for treating epithelial tissue damage comprising an RNA polynucleotide antisense to a sequence comprised by the glucosylceramide synthase mRNA in a pharmaceutically acceptable carrier. In fact, *Deng* lacks a disclosure of any composition suitable for treating epithelial tissue, as in the claimed invention. Rather, *Deng* discloses a DNA composition for preparing stable transfectants of cultured MEB4 cells. MEB4 cells are cultured melanoma cells in contrast to epithelial tissue or skin, as in the present invention. While *Deng's* DNA compositions purportedly were used to transfect melanoma cells in an *in vitro* culture, *Deng* fails to disclose or suggest any therapeutic composition for use *in vivo* with epithelial tissue. Moreover, the *Deng* DNA composition consists of a cDNA fragment encoding glucosyl-ceramide synthase cloned into the pCI-neo expression vector in both orientations relative to the CMV promoter in contrast to RNA, as in the present invention. Neither, *Neida* nor *Balreira* provide further evidence in this regard. Thus, it is submitted that Claims 1, 2, 6 and 8 are patentable over *Deng*.

Claims 3 and 7 stand rejected under 35 U.S.C. § 112, first paragraph, for failing to meet the written description requirement. The Office action took the position that the claims included new matter. Applicants request that this rejection be reconsidered and withdrawn for the following reasons. Although it is well settled that a claimed invention does not have to be described *ipsis verbis* in the specification, in this particular case there is *ipsis verbis* support. In

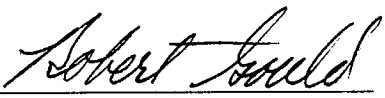
particular, at page page 10, lines 11-12 and lines 13-24. The sequences of these RNA molecules includes sequences that are antisense to the sequence of the glucosylceramide synthase mRNA. (See page 10 lines 16-18). Thus, with respect to sequence information, the sequence of the target mRNA is known. (See page 10 lines 19-21) Moreover, as set forth previously oligonucleotide design for RNAi knockouts is well established once a target is identified. While it may not be the case that every RNAi oligonucleotide will necessarily work for its intended purpose it is a virtual certainty that if several are made one or more will work. This is not undue experimentation. The specification also clearly sets forth how glucosylceramide synthase is tied into the overall scheme. As pointed out on page 7 lines 26-30, epithelial cell homeostatsis is regulated via lipids by means of ceramides and glucoceramides. Further, the specification at page 10, lines 13-24 discloses that ceramide and glucose ceramide concentrations can be modified so that they exert the desired effect on the CD_{1d} molecule. The specification indicates that reducing glucosylceramide synthase transcripts is one method for doing this and that one method for doing this is to use antisense cRNA molecules, including RNAi. (Specification, page 10, lines 13-24). Thus, it is believed that the use of antisense RNA oligonucleotides and RNAi oligonucleotides in particular is properly supported by the specification and Applicants respectfully request that the rejection be withdrawn.

The Office action also took the position that the specification did not enable the compositions for preventing anything other than epithelial tissue damage caused by melanoma formation. However, the specification clearly teaches that epithelial cell homeostasis can be maintained through the regulation of ceramides and glucosylceramides. (See specification page 10, lines 13-14). The background teaches that by blocking endogenous CD_{1d} function in epithelial cells protects the skin from unfavorable influences encountered in the environment, particularly from oxidative stress or sun radiation. (See specification at page 5, lines 12-16) Further, the specification teaches that by modifying or blocking CD_{1d} function prevents the detrimental effect of stress, including UV radiation-induced skin damage, e.g., as a result of burning, epidermal hyperplasia, mutant p53 accumulation, inflammation, immune suppression and skin aging, in addition to preventing the induction of cancer. (See specification at page 7, l;ines 5-14). Further, blocking CD_{1d} causes damaged epithelial cells to die and be replaced by healthy epithelial cells. (See specification page 8, lines 14-18). Similarly, the specification

points out that GlcCer induces cell proliferation and inhibits programmed cell death. (See specification page 8, lines 5-6). Thus, the specification discloses in detail that epithelial tissue damage can be treated or prevented using the disclosed methods.

Applicants submit that they have made an earnest effort to place the application in allowable form and request that the amendments be entered and considered and that the application be passed to issue. Should the Examiner become aware of any issues that could be resolved telephonically the Examiner is encouraged to contact the undersigned attorney. The Commissioner is hereby authorized to charge deposit account 02-1818 for any fees which are due and owing.

Respectfully submitted,
BELL, BOYD & LLOYD LLP

BY 
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